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Proposed Registration Decision PRD2013-04

p-Menthane-3,8-diol and Related Oil of Lemon Eucalyptus Compounds

(publié aussi en français)

28 March 2013

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2013-4E (print version)
H113-9/2013-4E- PDF (PDF version)

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Overview

Proposed Registration Decision for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale of the technical p-menthane-3,8-diol and related oil of lemon eucalyptus compounds (sold under the trade name Citriodiol), and the personal insect repellents Citrepel Insect Repellent 30 and Natrapel Insect Repellent, containing the technical grade active ingredient p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, for use to repel mosquitoes.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health and value assessments of p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, Citrepel Insect Repellent 30 and Natrapel Insect Repellent containing p-menthane-3,8-diol and related oil of lemon eucalyptus compounds.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What is p-menthane-3,8-diol and related oil of lemon eucalyptus compounds?

Citriodiol (p-menthane-3,8-diol and related oil of lemon eucalyptus compounds) is used to formulate skin-applied personal insect repellents. The mode of action of p-menthane-3,8-diol and related oil of lemon eucalyptus compounds for repelling mosquitoes is not known. However, in laboratory studies p-menthane-3,8-diol and related oil of lemon eucalyptus compounds has been seen to repel mosquitoes as they approach the zone near the treated skin, rather than act as a masking agent so that they do not find the host.

Health Considerations

Can approved uses of p-menthane-3,8-diol and related oil of lemon eucalyptus compounds affect human health?

p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds is unlikely to affect human health when it is used according to label directions.

Potential exposure to p-menthane-3,8-diol and related oil of lemon eucalyptus compounds may occur when handling and applying the end-use products, Citrepel Insect Repellent 30 and Natrapel Insect Repellent, which are proposed as personal insect repellents for repelling mosquitoes. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

In laboratory animals, p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, was of low acute toxicity via the oral and dermal routes of exposure, and slightly acutely toxic via

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

inhalation exposure. It was also a slight skin irritant, a moderate eye irritant, and not a skin sensitizer. Consequently, the hazard signal words, 'WARNING – EYE IRRITANT' and 'CAUTION POISON' are required on the label. The two end-use products are expected to be of low acute toxicity via the inhalation route of exposure but otherwise have similar toxicity profiles to the technical grade active ingredient. Consequently, the labels for the two end-use products require the hazard signal words, 'WARNING – EYE IRRITANT'. Based on the container sizes for the two end-use products, it is possible that a young child could consume enough of either product to experience significant toxicity. Therefore, for container sizes of 75 mL or larger, the hazard signal words, 'CAUTION POISON' are required on the labels.

Risks in Non-Occupational/Consumer Environments

Estimated risk for non-occupational / consumer exposure is not of concern provided that directions specified on the label are observed.

Exposure to individuals coming in contact with Citrepel Insect Repellent 30 and/or Natrapel Insect Repellent is not expected to result in unacceptable risk when used according to the label directions.

Precautionary (for example, use only on children 3 years of age or older) and hygiene statements on the label are considered sufficient to protect individuals from any unnecessary risk due to consumer exposure.

Environmental Considerations

An environmental assessment was not required for the proposed use as a personal insect repellent.

Value Considerations

What is the value of Citrepel Insect Repellent 30 and Natrapel Insect Repellent?

Citrepel Insect Repellent 30 and Natrapel Insect Repellent are skin-applied insect repellents that repel mosquitoes for 4 to 6 hours following application. These products will provide additional choice for mosquito repellent users.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Citrepel Insect Repellent 30 and Natrapel Insect Repellent to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

The signal words 'WARNING-EYE IRRITANT', 'CAUTION POISON', and 'PREVENT ACCESS BY UNAUTHORIZED PERSONNEL' are required on the principal display panel for the technical grade active ingredient label. The statements, 'PREVENT ACCESS BY UNAUTHORIZED PERSONNEL. Causes eye irritation. DO NOT get in eyes. Harmful if inhaled. Avoid inhaling or breathing sprays.' are required for the PRECAUTIONS section of the secondary display panel for the technical grade active ingredient.

The signal words, 'WARNING-EYE IRRITANT' and 'KEEP OUT OF REACH OF CHILDREN' are required on the principal display panels of the labels for the two end-use products and the signal words 'CAUTION POISON' are also required on the principal display for end-use products sold in containers 75 mL or larger in size. The statements, 'KEEP OUT OF REACH OF CHILDREN. Causes eye irritation. DO NOT get in eyes. are required for the PRECAUTIONS section of the secondary display panels on the labels for the two end-use products. For container sizes of 75 mL or larger, the statement, 'Harmful if swallowed' is also required on the secondary display panels of the labels for the two end-use products.

Since Citrepel Insect Repellent 30 and Natrapel Insect Repellent are applied directly to the skin, the secondary display panel of both end-use product labels must state 'Apply sparingly, not under clothing and only when necessary', 'After returning from the outdoors, wash product from all exposed skin and wash contaminated clothing', 'Do not allow children to apply this product to themselves', and 'Do not apply to the hands of children.' The precautionary statement 'DO NOT use on children under 3 years of age' is required on the secondary display panel of both Citrepel Insect Repellent 30 and Natrapel Insect Repellent.

Next Steps

Before making a final registration decision on p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on p-menthane-3,8-diol and related oil of lemon eucalyptus compounds (based on the Science Evaluation Section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

p-Menthane-3,8-diol and related oil of lemon eucalyptus oil compounds

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance

Function Insect repellent

Chemical name

1. **International Union of Pure and Applied Chemistry (IUPAC)** no IUPAC name assigned
2. **Chemical Abstracts Service (CAS)** Oils, eucalyptus, E. citriodora, hydrolyzed, cyclised

CAS number 1245629-80-4

Molecular formula N/A

Molecular weight N/A

Structural formula N/A

Purity of the active ingredient 100%

1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product

Technical Product—p-menthane-3,8-diol and related oil of lemon eucalyptus compounds (Citriodiol)

Property	Result
Colour and physical state	Pale yellow, liquid
Odour	Faint citrus odour
Melting range	N/A
Boiling point or range	267°C ± 0.5 at 103.63 kPa
Density	0.93–0.99 g/mL
Vapour pressure at 25°C	0.0638 Pa

Property	Result
Ultraviolet (UV)-visible spectrum	$\lambda_{max} < 300$ nm
Solubility in water at 25°C	670.7 mg/L
Solubility in organic solvents at 20°C (g/100 mL)	Solvent — Solubility (g/L) n-hexane — > 250 acetone — > 250
n-Octanol–water partition coefficient (K_{ow})	$\log K_{ow} = 2.42$
Dissociation constant (pK_a)	N/A
Stability (temperature, metal)	Determined to be thermally stable and stable under air and nitrogen when heated to a temperature of 150°C

End-use Products

Property	Citrepel Insect Repellent 30	Natrapel Insect Repellent
Colour	Medium yellow	Medium yellow
Odour	Lemon eucalyptus and alcohol odour	Lemon eucalyptus and alcohol odour
Physical state	Liquid	Liquid
Formulation type	Solution	Solution
Guarantee	30%	30%
Container material and description	Plastic (HDPE) liquid dispenser; lotion or pump spray top; 10 to 1000 mL capacity	Plastic (HDPE) liquid dispenser; lotion or pump spray top; 10 to 1000 mL capacity
Specific gravity	0.890–0.930	0.890–0.930
pH of 1% dispersion in water	6.5–7.5	6.5–7.5
Oxidizing or reducing action	N/A	N/A
Storage stability	Stable when stored for one year at ambient temperature in commercial packaging.	Stable when stored for one year at ambient temperature in commercial packaging.
Corrosion characteristics	Not corrosive to the container material.	Not corrosive to the container material.
Explodability	Not explosive	Not explosive

1.3 Directions for Use

Apply to exposed skin and clothing. Repels mosquitoes for 4 to 6 hours.

1.4 Mode of Action

The mode of action of p-menthane-3,8-diol and related oil of lemon eucalyptus compounds for repelling mosquitoes is not known. However, in laboratory studies p-menthane-3,8-diol and related oil of lemon eucalyptus compounds has been seen to repel mosquitoes as they approach the zone near the treated skin, rather than act as a masking agent so that they do not find the host

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in the technical product, p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the p-menthane-3,8-diol in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds consisting of toxicity studies and waiver rationales was conducted. The scientific quality of the data is acceptable and the database is considered sufficiently complete to define the majority of the toxic effects that may result from exposure to p-menthane-3,8-diol and related oil of lemon eucalyptus compounds.

The applicant submitted acute oral and dermal toxicity, irritation (eye and skin), sensitization, short-term toxicity, developmental toxicity, and mutagenicity studies on p-menthane-3,8-diol and related oil of lemon eucalyptus compounds. A data waiver rationale was submitted requesting that the acute inhalation toxicity data requirements be addressed by a study of the acute inhalation toxicity of an insect repellent formulation containing 40% p-menthane-3,8-diol and related oil of lemon eucalyptus compounds. A data waiver rationale was also submitted requesting that the acute toxicity information requirements for the two end-use products be addressed by the studies submitted for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds.

p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds is of low acute toxicity via the oral and dermal routes of exposure, and slightly toxic via inhalation. It is a moderate eye irritant, a slight skin irritant, and it is not a skin sensitizer. The data waiver rationale to bridge the acute toxicity studies for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds to address the acute toxicology data requirements for the two end-use products was accepted.

Citrepel Insect Repellent 30 and Natrapel Insect Repellent have the same acute toxicity profile as p-menthane-3,8-diol and related oil of lemon eucalyptus compounds with the exception that they are considered to be of low acute toxicity via the inhalation route of exposure

Short-term toxicity studies provided for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds included 14 and 28 day repeated dose dermal toxicity studies in rats. In the 14 day study, a lowest observed adverse effect level (LOAEL) of 3000 mg/kg bw/day (lowest dose tested) for dermal and systemic toxicity was identified based on skin irritation effects at the site of application and clinical signs of toxicity. Mortalities, more severe clinical signs of toxicity (for example, hypoactivity, tremors, postural and gait changes), decreased body weights and increased liver weight changes were observed at the highest dose tested, 5000 mg/kg bw/day which resulted in an early termination of dosing in this group. A single dose of 1000 mg/kg bw/day was administered in the 28 day study and was determined to be the no observed adverse effect level (NOAEL) for systemic toxicity and the LOAEL for dermal toxicity based on skin irritation at the site of application.

Developmental toxicity testing included two studies of p-menthane-3,8-diol and related oil of lemon eucalyptus compounds administered by gavage to female rats during gestation and lactation, and a third study of dermal administration to rats during gestation. In both oral studies the NOAEL for developmental toxicity was 1000 mg/kg bw/day (highest dose tested) with no effects observed on the incidences of alterations, malformations, or variations in the developing young. The NOAEL for maternal toxicity in the first study was 300 mg/kg bw/day based on clinical signs of toxicity and decreased body weights and weight gains at the highest dose tested. For the second oral study, the NOAEL for maternal toxicity was 500 mg/kg bw/day based on increased severity of clinical signs, decreased body weights and weight gains, and reductions in the total and number of live pups per litter in the 1000 mg/kg bw/day dose group. A single limit dose of 1000 mg/kg bw/day was applied in the dermal developmental toxicity study and was considered to be the LOAEL for maternal dermal and systemic toxicity based on skin irritation at the site of application and reductions in body weight gains. No treatment related developmental toxicity was observed in the study, and as a result the NOAEL for developmental toxicity is considered to be 1000 mg/kg bw/day.

p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds was not mutagenic when tested in a reverse mutation assay conducted in multiple strains of *Salmonella* Typhimurium and in a mouse lymphoma forward mutation assay. The technical grade active ingredient also gave negative results in a chromosomal aberration test in human lymphocytes in vitro and in an in vivo mouse micronucleus assay.

3.2 Occupational and Bystander Risk Assessment

3.2.1 Use Description /Exposure Scenario

The proposed domestic use of Citrepel Insect Repellent 30 and Natrapel Insect Repellent is as a pump/trigger spray to repel mosquitoes. The end-use products are to be applied sparingly to exposed skin and reapplied in 4 to 6 hours if necessary. Citrepel Insect Repellent 30 and/or Natrapel Insect Repellent should not be applied more than twice in a day.

3.2.2 Dermal Absorption

In vitro dermal absorption studies in the pig and rat submitted by the applicant suggest that the components of p-menthane-3,8-diol and related oil of lemon eucalyptus compounds are volatile and poorly absorbed by the skin. The data, however, were considered to be supplemental and inconclusive with respect to the potential for components of p-menthane-3,8-diol and related oil of lemon eucalyptus compounds to be absorbed by the skin of treated individuals. Therefore, the application of either of the Citrepel Insect Repellent 30 and Natrapel Insect Repellent under clothing is not supported.

3.2.3 Occupational Exposure and Risk Assessment

Citrepel Insect Repellent 30 and Natrapel Insect Repellent are ready-to-use domestic use products. Occupational exposure and the associated risk assessment is not applicable.

3.2.4 Consumer Exposure and Risk Assessment

Exposure of consumers to Citrepel Insect Repellent 30 and Natrapel Insect Repellent is characterized as short- and intermediate in duration, and predominantly via the dermal and inhalation routes. Citrepel Insect Repellent 30 and Natrapel Insect Repellent contain p-menthane-3,8-diol and associated oil of lemon eucalyptus compounds at a guarantee of 30.0% by weight.

Since insect repellents are applied directly to the skin, exposure is considered to be very high. Typically, insect repellents are used intermittently during the biting insect season and are expected to be applied sparingly and only when biting insects are present. Depending on the insect biting-pressure and the concentration of the active ingredients, insect repellents are generally applied once to several times per day. Citrepel Insect Repellent 30 and Natrapel Insect Repellent, however, are proposed for use only once or twice daily (assuming a 4–6 hour protection time per application for a maximum of 12 hours of protection per day).

Potential exposure would occur in three population groups: adults, children and toddlers. For all populations, two dermal exposure scenarios were identified for risk assessment purposes of personal insect repellents: acute (occasional use) and intermediate (prolonged seasonal use). For toddlers, one additional exposure scenario was identified: non-dietary oral exposure resulting from transfer of residues from the skin to the mouth from hand-to-mouth activities.

Since no toxicological endpoints of concern were identified, a quantitative risk assessment was not conducted for the proposed use. The potential exposure to p-menthane-3,8-diol and related oil of lemon eucalyptus compounds is considered to be very high since it is applied directly to the skin, can be applied twice per day, and can be used frequently throughout the summer months in Canada.

Based on the results of the toxicology studies conducted with p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, in which no toxicological endpoints of concern were identified, no adverse effects are expected to occur from the proposed use of Citrepel Insect Repellent 30 or Natrapel Insect Repellent when applied in accordance with the label instructions.

The use of these products in very young children, however, will be restricted in the absence of further information to fully address potential sensitivity to the young. Consequently, these products will not be permitted for use on children under three years of age.

3.3 Incident Reports Related to Human and Animal Health

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched and reviewed for the active, p-menthane-3,8-diol and related oil of lemon eucalyptus compounds.

As of October 18, 2012, no health-related incident reports for products containing p-menthane-3,8-diol and related oil of lemon eucalyptus compounds were received by the PMRA. There were also no health-related incidents reported by the USEPA. In the California Pesticide Illness Surveillance Program, there was one case of a probable association with exposure to p-menthane-3,8-diol and related oil of lemon eucalyptus compounds in which a three year old child accidentally sprayed an insect repellent containing the technical grade active ingredient in his eyes and experienced eye irritation. This observation is consistent with the available toxicological database for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds.

The applicant submitted information on cases of adverse reactions associated with the use of insect repellent products containing p-menthane-3,8-diol and related oil of lemon eucalyptus compounds in the UK and the US. Few cases were reported to be severe, the majority involved skin rash, burning sensation/irritation, and/or skin sensitization, and based on the information supplied, they represent a very small fraction of the total units of these products sold.

As of December 4, 2012 there were five incident reports submitted to the PMRA related to PMK, a synthetic form of p-menthane-3,8-diol. Four reports were for human incidents, one was a companion animal incident, and all of them related to insect repellent products containing 10% PMK. The human incidents were minor to moderate and all involved immediate or delayed signs of skin irritation and/or skin sensitization following dermal application of the insect repellent. In the animal incident, a dog was reported to have edema around the eyes after ingesting an insect repellent containing PMK after biting into a bottle. In all cases, the symptoms resolved after removing the source of exposure, and following medical treatment.

4.0 Impact on the Environment

An environmental assessment was not required for use as a personal insect repellent.

5.0 Value

5.1 Effectiveness Against Pests

A total of 4 studies consisting of field and laboratory trials were reviewed in support of these products. Three of these studies were conducted in California, and one was conducted in England. Over the course of these studies, 30% p-menthane-3,8-diol and related oil of lemon eucalyptus compounds were tested as a skin-applied mosquito repellent against 7 species of mosquitoes, including *Ochlerotatus melanimon, Aedes vexans, Ochlerotatus increpitus, Anopheles freeborni, Culex tarsalis, Aedes aegypti,* and *Culex quinquifasciatus.* These studies demonstrated a complete protection time ranging from 4 to 6 hours. Based on the submitted data, a claim of repels mosquitoes for 4 to 6 hours is supported.

5.1.1 Acceptable Efficacy Claims

Repels mosquitoes for 4 to 6 hours

5.2 Sustainability

5.2.1 Survey of Alternatives

Active ingredients currently registered in personal insect repellents for use against mosquitoes include: DEET; p-menthane-3,8-diol; metofluthrin; icaridin; soybean oil; citronella; and a 3% mixture of citronella, citrus, eucalyptus, pine, geranium and camphor essential oils.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act.*

p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds and the two end-use products, Citrepel Insect Repellent 30 and Natrapel Insect Repellent were assessed in accordance with the PMRA Regulatory Directive DIR99-03:[5]

- p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds does not meet the Track 1 criteria as the active ingredient is not highly toxic, and is not expected to be persistent in the environment or to bioaccumulate.

- There are also no formulants, contaminants or impurities present in the end-use products, Citrepel Insect Repellent 30 and Natrapel Insect Repellent that would meet the TSMP Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds, Citrepel Insect Repellent 30 and Natrapel Insect Repellent do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an on-going basis through PMRA formulant initiatives and DIR2006-02.

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5 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-11-30) pages 2641-2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613: *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*

8 Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds is sufficiently complete to define the majority of toxic effects that may result from exposure to p-menthane-3,8-diol and related oil of lemon eucalyptus compounds. p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds are of low acute toxicity via the oral and dermal routes of exposure, and slightly acutely toxic via inhalation exposure. It is a slight skin irritant, a moderate eye irritant, and it is not a dermal sensitizer. p-Menthane-3,8-diol and related oil of lemon eucalyptus compounds is considered to be non-mutagenic. Citrepel Insect Repellent 30 and Natrapel Insect Repellent are expected to have very similar toxicological profiles to Citriodiol with the exception that they are expected to have low acute inhalation toxicity.

Both Citrepel Insect Repellent 30 and Natrapel Insect Repellent are to be applied sparingly, not under clothing and only when necessary. After returning from the outdoors, users are instructed to wash all treated skin areas and to wash contaminated clothing before re-use. In order to further minimize exposure to young children, product labels instruct users to not permit children to apply the products to themselves and to not apply product to the hands of children or on children under three years of age.

Exposure to individuals handling and/or being applied with Citrepel Insect Repellent 30 or Natrapel Insect Repellent is not expected to result in unacceptable risk when used according to label directions.

7.2 Value

Citrepel Insect Repellent 30 and Natrapel Insect Repellent are skin-applied insect repellents that repel mosquitoes for 4 to 6 hours following application. These products will provide additional choice for mosquito repellent users.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of the technical product, p-menthane-3,8-diol and related oil of lemon eucalyptus compounds (Citriodiol) and the end-use products, Citrepel Insect Repellent 30 and Natrapel Insect Repellent, containing p-menthane-3,8-diol and related oil of lemon eucalyptus compounds, to repel mosquitoes.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health.

List of Abbreviations

µg	micrograms
bw	body weight
CAS	Chemical Abstracts Service
EP	end-use product
g	gram
GD	gestation day
HDPE	high density polyethylene
hr	hour
i.p	intraperitoneal
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	*n*–octanol-water partition coefficient
kPa	kilo Pascal
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
MAS	maximum average score
MGMS	maximum group mean score
mg	milligram
mL	millilitre
MMAD	mass median aerodynamic diameter
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NCE	normochromatic erythrocyte
nm	nanometre
NOAEL	no observed adverse effect level
Pa	Pascal
PCE	polychromatic erythrocyte
PII	primary irritation index
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
UK	United Kingdom
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Summary of acute toxicity, short-term toxicity, developmental toxicity, and mutagenicity information for p-menthane-3,8-diol and related oil of lemon eucalyptus compounds (Citriodiol)

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
Acute oral toxicity Exposure by gavage	Rat – Sprague Dawley (5/sex/group), 1414, 2000, 2828 mg/kg bw	LD_{50} (♂+ ♀) = 2408 mg/kg bw **Low acute toxicity**	Ataxia, coma, hunched posture, lethargy, ptosis; reduced, laboured, and noisy respiration. Animals that died during the study had dark livers and kidneys, and hemorrhagic lungs, gastric mucosa, and small intestines, and one animal had a hemorrhagic large intestine.	2000780
Acute dermal toxicity Semi-occluded exposure, 24 hr	Rat – Sprague Dawley (5/sex) 2000 mg/kg bw, limit test	LD_{50} (♂+ ♀) > 2000 mg/kg bw **Low acute toxicity**	No mortality occurred.	2000783
Acute inhalation toxicity whole-body exposure chamber, 4 hr	Rat – Sprague Dawley (5/sex), 2.06 mg/L Repel Natural Aerosol (equivalent to 0.83 mg/L Citriodiol)[a], MMAD[b]: 2.35-2.56	LC_{50} (♀ + ♂) > 0.83 mg/L **Slight acute toxicity**	No mortality occurred.	2000784
Eye Irritation Draize method	Rabbit – New Zealand White (2♂ + 4♀) Dose: 0.1 mL of test substance. Eyes were left unwashed.	MGMS[c] = 32.8 MAS[d] = 31.9 **Moderately irritating**	Iritis and conjunctivitis cleared by 7 days, corneal opacity cleared by 14 days.	2000785

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
Dermal Irritation Draize method, semi-occluded exposure, 4 hr	Rabbit – New Zealand White (4♂ + 2♀) Dose: 0.5 mL	PII[c] = 1.2 MAS[d] = 1.1 **Slightly irritating**	Very slight to well-defined erythema cleared by 7 days and very slight edema cleared by 72 hr.	2000787
Dermal Sensitization Guinea Pig Maximization	Guinea Pig – Dunkin Hartley (30♀, 10 control/20 test) Intradermal induction (0.1 mL): Freund's adjuvant/water 1:1, 5% in arachis oil, 5% in Freund's adjuvent + arachis oil Topical induction (0.2-0.3 mL): undiluted Topical challenge (0.1-0.2 mL): undiluted or 75% in arachis oil	Negative results. Not a dermal sensitizer.	No positive reactions were observed following challenge in any test or negative control animals.	2000788
Bacterial reverse mutation assay Plate incorporation test	*Salmonella* Typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and *Escherichia coli* strain WP2uvrA Experiment 1: 0, 8, 40, 200, 1000, 5000 µg/plate Experiment 2: 0. 312.5, 625, 1250, 2500, 5000 µg/plate Both tests with and without metabolic activation.	Non-mutagenic	No significant increases in revertant colonies for any strain, at any dose level with or without metabolic activation. No toxicity to any strains of *S.* Typhimurium; decrease in revertant frequency at high concentrations.	2000803

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
Gene mutation in mammalian cells in vitro	L5178Y TK$^{+/-}$ mouse lymphoma cell line Initial assay: 0, 50, 75, 100, 150, 175, 200, 210 µg/mL without metabolic activation; 0, 50, 75, 100, 150, 200, 250, 275, 300, 325 µg/mL with metabolic activation Confirmatory assay: 0, 50, 75, 100, 150, 225 µg/mL without metabolic activation; 0, 250, 275, 300, 310, 320, 330, 340, 350 µg/mL with metabolic activation	Non-mutagenic	None of the concentrations tested induced a mutation frequency above background with or without metabolic activation. In both assays, cytotoxicity ranged from none at the lowest concentration to moderate or high at the highest concentration with and without activation.	2000804
In vitro mammalian chromosomal aberration assay	Human lymphocytes in culture Experiment 1: 0, 53.84, 107.69, 215.38, 430.75, 861.5, 1723 µg/mL 4 hr exposure/20 hr incubation with and without metabolic activation Experiment 2: 0, 26.92, 53, 84, 107.69, 161.53, 215.38, 430.75 µg/mL 24 hr exposure without metabolic activation; 0, 107.69, 215.38, 430.75, 861.5, 1292.25, 1723 µg/mL 4 hr exposure/20 hr incubation with metabolic activation	Non-mutagenic.	No significant increases in chromosomal aberrations and polyploidy with and without metabolic activation. Cytotoxicity (decreased mitotic index) observed at mid to high concentrations without metabolic activation and at high concentrations with metabolic activation.	2000805

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
In vivo mammalian cytogenetics (bone marrow micronuclei)	Mouse – CD-1 (6♂/harvest time/group); 0, 250, 500, 1000 mg/kg bw i.p. in corn oil. Bone marrow harvested at 24 hr for two lowest dose groups, and 24 and 48 hr for 1000 mg/kg bw group.	Non-mutagenic	No statistically significant increases in bone marrow micronuclei at any dose level and timepoint. ≥ 500 mg/kg bw: Prostration, laboured breathing, ataxia, hypoactivity; 1000 mg/kg bw: 8/18 deaths. No cytoxicity to bone marrow at any dose (no change in PCE/NCE[f]).	2000806
Short-term dermal toxicity 14 day semi-occlusive application	Rat – Sprague Dawley (15♀/group). 0, 300, 5000 mg/kg bw/day in mineral oil, 6 hr/day, 7 days/week.	LOAEL (dermal and systemic toxicity) = 3000 mg/kg/bw/day.	5000 mg/kg bw/day: clinical signs of toxicity, ↓ body weights/weight gains, ↑ absolute/relative liver weights. ≥ 3000 mg/kg bw/day: erythema and desquamation at dosing site; clinical signs of toxicity.	2000790
Short-term dermal toxicity 28 day semi-occlusive application	Rat – Sprague Dawley (10/sex/group). 0, 1000 mg/kg bw/day in mineral oil (limit test), 6 hr/day, 7 days/week.	NOAEL (systemic toxicity) = 1000 mg/kg bw/day LOAEL (dermal toxicity) = 1000 mg/kg bw/day.	1000 mg/kg bw/day: skin irritation (erythema, edema, desquamation) and histopathology (hyperplasia/hyperkeratosis of epidermis, hyperplasia of sebaceous glands, inflammatory cell infiltration of dermis) at site of application.	2000794
Developmental toxicity – oral Exposure by gavage	Rat – Sprague Dawley (25♀/group). 0, 100, 300, 1000 mg/kg bw/day in corn oil, gestation days 6-20.	Maternal NOAEL = 300 mg/kg bw/day. LOAEL = 1000 mg/kg bw/day. Developmental NOAEL = 1000 mg/kg bw/day.	Maternal: 1000 mg/kg bw/day: clinical signs of toxicity, ↓ body weights (GD[g] 7-9), ↓body weight gains (GD 6-9, 18-21), ↓ absolute/relative feed consumption (GD 6–9) Developmental: No treatment related developmental toxicity at	20007999

STUDY	SPECIES/STRAIN AND DOSES	RESULT	TARGET ORGAN / SIGNIFICANT EFFECTS / COMMENTS	REFERENCE
			any dose tested.	
Developmental toxicity – oral Exposure by gavage	Rat – Sprague Dawley (10♀/group). 0, 50, 100, 500, 1000 mg/kg bw/day in corn oil from gestation day 6 to lactation day 3.	Maternal: NOAEL = 500 mg/kg bw/day. LOAEL = 1000 mg/kg bw/day. Developmental: NOAEL = 1000 mg/kg bw/day.	Maternal: 1000 mg/kg bw/day: clinical signs of toxicity, ↓ body weights/weight gains, ↓ total and live pups/litter at birth. Developmental: No treatment related developmental toxicity at any dose tested.	2000797
Developmental toxicity – dermal Semi-occlusive application	Rat – Sprague Dawley (25 ♀/group). 0, 1000 mg/kg bw/day in mineral oil (limit test), 6 hr/day, 7 days/week on gestation days 6-20.	Maternal: LOAEL (dermal and systemic toxicity) = 1000 mg/kg bw/day. Developmental: NOAEL = 1000 mg/kg bw/day.	Maternal: Erythema, edema, desquamation at site of application; decreased body weight gains. Developmental: No related developmental toxicity.	2000800

[a] Repel Natural Aerosol contains 40% Citriodiol
[b] MMAD = mass median aerodynamic diameter
[c] MGMS = maximum group mean score
[d] MAS = maximum average score for 24, 48, and 72 hr
[e] PII = primary irritation index
[f] PCE/NCE = ratio of polychromatic erythocytes to normochromatic erythrocytes
[g] GD = gestation day

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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2000764	2010, CAS # Assignment, DACO: 2.6
2000766	1999, A practical and efficient synthesis of p-menthane-3,8-diols., DACO: 2.11, 2.11.1, 2.11.2, 2.11.3, 2.11.4
2000767	1999, [CBI removed] of Citriodiol, DACO: 2.13, 2.13.1 CBI
2000768	2010, Analytical Methodology & Confirmation of Identity summary, DACO: 2.13.1, 2.13.2 CBI
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2000770	1998, [CBI removed]: physical and chemical characteristics data volume, DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9
2000771	2006, Citriodiol: determination of general physico-chemical properties, DACO: 2.14.13, 2.14.5, 2.14.8, 2.16 CBI
2287051	2009, PMDRBO: Estimation of the of the vapour pressure, water solubility and octanol / water partition coefficients (revised), DACO: 2.14.11, 2.14.7, 2.14.9 CBI
2140560	2011, Description of Starting Materials, DACO: 2.11.2 CBI
2140561	2011, Detailed Production Process Description, DACO: 2.11.3 CBI
2140562	2011, Determination of [CBI removed] content in a specimen of citriodora oil, DACO: 2.12 CBI
2140563	2011, Methodology/Validation, DACO: 2.13.1 CBI
2140564	2011, Batch Data, DACO: 2.13.3 CBI
2140565	2011, Impurities of Heath Concern, DACO: 2.13.4 CBI
2140567	2011, Storage Stability Data, DACO: 2.14.14 CBI
2140569	2011, Effect of Reducing or Removing the Concentration of [CBI removed] in PMDRBO technical, DACO: 2.16 CBI

2140571	2011, Effect of Reducing or Removing the Concentration of [CBI removed} in PMDRBO technical, DACO: 2.16 CBI
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2204306	2012, DACO 2.13.1 Supplement, DACO: 2.13.1 CBI
2204307	2012, DACO 2.13.1 Supplement, DACO: 2.13.1 CBI
2204308	2012, Replacement 5 Batch Data, DACO: 2.13.3 CBI
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2000891	2004, Mosi-guard (Citrepel 30) GC Report - Multiple Production Batches, DACO: 3.4.1 CBI
2000892	2005, Physical and chemical properties determination, Repel Insect Repellent 30LE, DACO: 3.5, 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.2, 3.5.3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
2000893	2006, Container stability determination real time and accelerated chemical stability, DACO: 3.5.10, 3.5.14, 3.5.5 CBI
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2141080	2011, Physical State, DACO: 3.5.2 CBI
2141081	2011, Odour, DACO: 3.5.3 CBI
2141082	2011, Container Material, DACO: 3.5.5 CBI
2141083	2011, Density or Specific Gravity, DACO: 3.5.6 CBI
2141084	2011, pH, DACO: 3.5.7 CBI
2141085	2011, Viscosity, DACO: 3.5.9 CBI
2141086	2011, Mosi-guard Natural Spray (30% PMDRBO) Formulation Testing, DACO: 3.5.1, 3.5.3, 3.5.4, 3.5.6, 3.5.7, 3.5.9 CBI
2141087	2011, Storage Stability, DACO: 3.5.10 CBI
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2141089	2011, Flammability, DACO: 3.5.11 CBI
2141090	2011, Flammability, DACO: 3.5.11 CBI
2141091	2011, Explodability, DACO: 3.5.12 CBI
2141092	2011, Corrosion Characteristics, DACO: 3.5.14 CBI
2142363	2011, Enforcement Analytical Method, DACO: 3.4.1 CBI
2142364	2011, Impurities of Health Concern, DACO: 3.4.2 CBI
2142366	2011, Colour, DACO: 3.5.1 CBI
2142367	2011, Physical State, DACO: 3.5.2 CBI
2142369	2011, Odour, DACO: 3.5.3 CBI
2142370	2011, Container Material, DACO: 3.5.5 CBI
2142371	2011, Density or Specific Gravity, DACO: 3.5.6 CBI
2142373	2011, pH, DACO: 3.5.7 CBI
2142374	2011, Viscosity, DACO: 3.5.9 CBI
2142375	2011, Mosi-guard Natural Spray (30% PMDRBO) Formulation Testing, DACO: 3.5.1, 3.5.3, 3.5.4, 3.5.6, 3.5.7, 3.5.9 CBI
2142376	2011, Storage Stability, DACO: 3.5.10 CBI
2142378	2011, Storage Stability, DACO: 3.5.10 CBI
2142379	2011, Flammability, DACO: 3.5.11 CBI
2142380	2011, Flammability, DACO: 3.5.11 CBI
2142381	2011, Explodability, DACO: 3.5.12 CBI
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2000774	2009, 4.1-2: Comprehensive Toxicology Summary - PMDRBO components: Group 1 Menthol and PMD, DACO: 12.7, 4.1
2000775	2009, 4.1-3: Comprehensive Toxicology Summary - PMDRBO components: Group 2 Isopulegol, DACO: 12.7, 4.1

2000776 2009, 4.1-4: Comprehensive Toxicology Summary - PMDRBO components: Group 3 PMD-Citronellal acetals, DACO: 12.7, 4.1

2000777 2009, 4.1-5: Comprehensive Toxicology Summary - PMDRBO components: Group 4 Citronellol, DACO: 12.7, 4.1

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2000897 2010, 5.1- Citrepel Insect Repellent 30 - EU Exposure Assess. - IIB 8 Exposure assessment, DACO: 5.1, 5.2, 5.7, 5.8

2000898 2003, Skin Penetration Test of Mosquito Protector MPCT 1502/KC01, DACO: 5.8

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2141093 2011, Request for Waiver, DACO: 4.6.1, 4.6.2, 4.6.3, 4.6.4, 4.6.5, 4.6.6

3.0 Value

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2142392	2003, Laboratory and Field Tests of the Effectiveness of the Lemon Eucalyptus Exract Citriodiol, DACO: 10.2.3
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2142399	1999, Field Test- Mosquito Repellent Efficacy/Duration of Wisconsin Pharmacal Company Formula, DACO: 10.2.3

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B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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ii) Unpublished Information

1.0 Human and Animal Health

PMRA Document Number	Reference
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